In the Claims

Please amend Claim 8 as follows:

C2

8. **(Twice amended)** A pharmaceutical composition comprising a recombinant adeno-associated virus (AAV) virion comprising a nucleotide sequence encoding a functional Factor VIII protein, wherein said recombinant adeno-associated virus virion lacks AAV *rep* and *cap* genes, and wherein said Factor VIII protein is B domain-deleted.

REMARKS

The Specification has been amended. Support for the amendment can be found in the Specification (page 54) of the U.S. Application No. 09/470,618 to which this Application claims priority. Claim 8 has been amended to better define the invention. Support for the amendment can be found in the Specification as filed (for example, on page 5, lines 9-11, and 19-26). Thus, Claims 8-17 and 19 are now presented for further consideration. The changes made to the Specification and Claim by the current amendments, including **[~~deletions~~]** and additions, are shown on the attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this Amendment. No new matter is being added herewith.

Submitted herewith is the new 1449 properly citing the patent No. 5,255,347 issue date 7/6/93.

Claim Objections

The Examiner objected to Claims 14 and 15 as being dependent upon a rejected base Claim 8. The Applicant has amended Claim 8, and requests withdrawal of the Claims objections.

Rejections under 35 U.S.C. § 102

The Examiner rejected Claims 8-10 and 19 under 35 U.S.C. § 102(e) for being allegedly anticipated by Dwarki *et al.* US patent No. 6,221,646. The Applicant respectfully disagrees. Dwarki *et al.* discloses a method of making AAV virions that comprise a heterologous gene, wherein the heterologous gene encodes a human protein, Factor VIII. The present invention discloses AAV virions that comprise a B domain-deleted Factor VIII (see, for example, page 5, lines 9-11, and 19-26), and yet are shown to express biologically

active Factor VIII. Thus, because Dwarki *et al.* does not teach a "B-domain deleted Factor VII", the Applicant respectfully requests withdrawal of the §102 rejections.

Rejections under 35 U.S.C. § 103

The Examiner rejected Claims 8, 9, 10, 16, 17, and 19 under 35 U.S.C. § 103(a) for being allegedly unpatentable over Chiorini *et al.* US patent No. 5,693,531 taken with Simonet US patent No. 6,268,212. More specifically, the Examiner believes that it would have been obvious at the time the invention was made to one of ordinary skill in the art to combine the teaching of Chiorini and Simonet to make a pharmaceutical composition comprising a recombinant AAV comprising a human Factor VIII subunit operably linked to a liver-specific promoter. The Examiner further argued that Dwarki *et al.* that teaches a method for producing "gutted" AAV virions comprising a nucleic acid sequence encoding a Factor VIII protein is presumed to be enabled by virtue of being a claim of a patent, and thus supports the presumption of validity of the production of an AAV virion comprising a nucleic acid encoding a functional Factor VIII protein taught by Chiorini. Applicant respectfully disagrees.

When a prior art reference merely discloses the structure of the claimed compound, evidence showing that attempts to prepare that compound were unsuccessful before the date of invention will be adequate to show inoperability. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1971). Moreover, the level of disclosure required within a reference to make an "enabling disclosure" is the same no matter what type of prior art is at issue. It does not matter whether the prior art reference is a U.S. patent or a printed publication (see, MPEP 2121).

The cited art fails to support a *prima facie* case of obviousness because neither reference contains an "enabling disclosure" of how to make a recombinant AAV virion comprising a human Factor VIII subunit operably linked to a tissue-specific promoter. Chiorini *et al.* lists Factor VIII as one of many therapeutic agents which may theoretically be placed in the AAV vector, but does not provide any enabling description of how to achieve this in practice. However, in order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method. *Motorola Inc. v. Interdigital Tech. Corp. (Fed. Cir. 1997).* In this case, aside from the

blanket statement that the DNA sequence may encode Factor VIII, Chiorini provides absolutely no enabling disclosure for achieving the claimed compositions.

Similarly, even though Dwarki *et al.* teaches a method for producing a gutted AAV vector comprising a gene encoding human Factor VIII, it does not contain an "enabling disclosure" because, at the time of filing, the art widely recognized that Factor VIII could not be packaged into rAAV, gutted or otherwise. For example, in 1997, Verma indicated that "to produce an AAV vector, the *rep* and *cap* genes are replaced with the transgene [ ] AAV vectors can accommodate only 3.5-4.0 kilobases of foreign DNA – this will exclude larger genes". (See page 241, column 3, lines 1-3, and 13-15). Even after applicants' priority date, Hortelano and Chang (cited by the Examiner) acknowledged: "Despite the promising results obtained with AAV vectors delivering hFIX, it has not yet been used to deliver FVIII. The genome of AAV is only 4.7 kb, too short to harbour the full-size hFVIII cDNA (7 kb). Even the truncated version of hFVIII (4.4 kb) obtained after removing the B domain is larger than the maximum genetic sequences that can be accommodated, highlighting the greater technical difficulty in expressing FVIII."

Although Chao *et al.* (Blood 2000, 95: 1594-1599) packaged B-domain-deleted Factor VIII in AAV after applicants' priority date, they indicated that prior to their findings this was not thought possible: "[because] B-domain-deleted hFVIII cDNA (BDD-hFVIII) is 4.4 kb [it was] not thought feasible for testing in rAAV." See also, Gnatenko *et al.* (Brit. J. Haematology 1999, **104**:27-36) asserting that their data "provide the first evidence that rAAV is an adaptable virus for FVIII delivery."

In this case, neither Chiorini nor Dwarki *et al.* provides any guidance whatsoever for overcoming AAV's widely known packaging limitation in order to package the Factor VIII gene in rAAV. Although B-domain-deleted constructs of Factor VIII were generally known at the time of filing, as demonstrated above, it was widely believed that such constructs could not be packaged and expressed using rAAV. Therefore, at least three references published after applicants filing date demonstrate that Chiorini *et al.* and Dwarki *et al.* are not enabling and further demonstrate that the presently claimed compositions are novel.

In making an obviousness rejection, the Examiner must consider the state of the prior art as a whole. In doing so in the present case, it is clear that the closest art at the time of filing taught away from the claimed invention. "In general, a reference will teach

away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553. As discussed above, at least three references published after applicants filing date indicate that FVIII could not be packaged in rAAV, gutted or full-size.

The cited art fails to teach all the claimed limitations

Another requirement for a *prima facie* case of obviousness is that the references, either alone or in combination, teach or suggest all of the limitations of the pending claims. As discussed above, neither Chiorini et al. nor Simonet or Dwarki *et al.* teaches that a B domain-deleted Factor VIII nucleotide sequence is inserted in the AAV vector to express a functional Factor VIII protein.

These references fail because neither contains an "enabling disclosure", or teaches all the limitations of the claimed invention. Because of these deficiencies, Applicants submit that the PTO has failed to articulate a *prima facie* case of obviousness, and as such, the present rejection of Claims 8, 9, 10, 16, 17, and 19 under 35 U.S.C. 103(a) should be withdrawn.

The Examiner further rejected Claims 8-13, and 19 under 35 U.S.C. § 103(a) for being allegedly unpatentable over Dwarki *et al.* US patent No. 6,221,646 taken with Almstedt *et al.* WO 91/09122. More specifically, the Examiner believes that it would have been obvious at the time the invention was made to one of ordinary skill in the art to combine the teachings of Dwarki and Almstedt to make a pharmaceutical composition comprising a recombinant AAV virion comprising a nucleotide sequence encoding functional Factor VIII taught by Almstedt. The Applicants respectfully disagree. As we argued before (see above), the art at the time of filing clearly teaches that even the B-domain deleted Factor VIII will not fit on AAV, gutted or otherwise. Therefore, the art did not provide a reasonable expectation of success. Therefore, Applicants submit that the PTO has failed to articulate a *prima facie* case of obviousness, and as such, the present rejection of Claims 8-13, and 19 under 35 U.S.C. 103(a) should be withdrawn.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are inapplicable to the present claims. Accordingly, Applicants request the expeditious allowance of the pending claims.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned at (949) 721-8088 (direct line), to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 15 Nov. 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

These data therefore show the in vivo expression of therapeutically effective amounts of human Factor VIII using single factor AAV vectors.

In the Claims

8. **(Twice amended)** A pharmaceutical composition comprising a recombinant adeno-associated virus (AAV) virion comprising a nucleotide sequence encoding a functional Factor VIII protein, wherein said recombinant adeno-associated virus virion lacks AAV rep and cap genes, and wherein said Factor VIII protein is B domain-deleted.